Remarks/Arguments

Claims 1, 4-8, 10-11, 13-15, 32 and 35 are pending in the application. All claims have been rejected. New claims 36-40 have been added. Support for Claims 36-37 can be found in the original claims 1, 3 and 8-10 and throughout the specification. Support for including "carboxy terminal domain" in Claims 36, 38 and 40 can be found on page 20, lines 8 through page 21 line 2. Support for Claim 38 can be found throughout the specification, particularly on page 15, lines 16 – 21 and page 20, line 8 through page 21 line 23. Support for Claim 39 can be found throughout the specification and in the definition of Dab1 on page 4 lines 22-25. Support for Claim 40 can be found throughout the specification, specifically on page 3, lines 25-29 and page 15 lines 16-17. Reconsideration and withdrawal of the rejection are respectfully requested in light of the amendments and following remarks.

Addition of New Claims

In numerous attempts to further prosecution of this application, Applicants considered the rejections the Examiner made in previous Office Actions and attempted to revise the claims based on these rejections and the Examiner's suggestions. Having failed in this prolonged good faith effort to reach a compromise with the Examiner, Applicants have now added back broad claims, to which we feel we are entitled, as new claims 36-40. Previous rejections by the Examiner and arguments made by Applicants relating to similar claims, and additional arguments relating to the new claims, are presented below in an effort to address all of the Examiner's concerns and expedite prosecution.

Claims 36 - 40

The terms Cdk5 and Dab1 were well known in the art at the time the present application was filed and sufficient to describe the invention.

Examiner's Arguments

Throughout prosecution of the present application, the Examiner rejected claims under 35 USC § 112, first and second paragraphs asserting that the recitation of "Cdk5" and "Dab1" is unclear as to the polypeptides that are meant to be encompassed by these terms. The Examiner has stated that there is no "clear definition" of the terms "Cdk5" and

"Dab1" in the specification and even though these terms may have been used in the art at the time of the invention, the definitions of the terms in the specification are not limited to those "Cdk5" and "Dab1" polypeptides that were known in the art at the time of the invention including genbank accession numbers 3288851 and 1771281. The Examiner stated that the specification fails to define which of the Dab1 and Cdk5 properties are necessary for inclusion of a cyclin-dependent kinase or a disabled-1 protein which is distinct in sequence from similar proteins that may share these characteristics.

Even though the Examiner acknowledged that Dab1 and Cdk5 were known in the art at the time of filing of the invention and further acknowledged that the claims were not drawn to the Dab1 or Cdk5 polypeptides themselves, he asserted that the terms must be limited to particular sequences to meet the requirement of definiteness.

Applicants' Arguments

The terms "Cdk5" and "Dab 1" were well known in the art as of the application filing date of February 19, 2002 and are described in the specification in a manner consistent with these meanings. The specification defines "Cdk5" as "a protein with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases"(p. 4) and defines "Dab1" as "an intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity" (p. 4). Applicants also include genbank accession numbers for human and mouse in the definition of Dab1 and human, mouse and rat genbank accession numbers for Cdk5. Applicants also included numerous references in the specification and during prosecution showing prior scientific publications that describe properties of Dab1 and Cdk5 which distinguish them from other cyclin dependent kinases and closely related Dab proteins. These terms are in fact creations of the art used to denote, in each case, a class of proteins with a unique set of features that allowed them to be grouped together and distinguished from other proteins. Furthermore, Dr. Thomas Curran, a co-inventor of the present application and a person of skill in the art provided an expert declaration stating that "Cdk5", "Dab1" and "Cdk5 serine kinase activity" were well known terms in the art at the time the application was filed (see response filed 4/25, 2005).

Applicants previously asserted and maintain that the invention is not based on the discovery of the Dab1 or Cdk5 proteins or their general activities which were well known.

The invention is instead based on the discovery that Dab1 is specifically phosphorylated by Cdk5. Applicants further asserted that Cdk5 activity is tightly controlled by its regulator, p35, making Cdk5 activity difficult to determine based on levels of Cdk5 present. Furthermore, a substrate which is selectively phosphorylated by Cdk5 had not heretofore been identified. The discovery that Dab1 is specifically phosphorylated on serine within a preferred candidate sequence by Cdk5 is the basis for the invention. The invention is not based on the novelty or nonobviousness of Cdk5 or Dab1, but rather on the special relationship between the two as taught for the first time in the present application. The invention claimed in the present application is directed to a unique method for determining Cdk5 serine kinase activity based on this special relationship.

In Falkner v. Inglis, ---F.3d---, 2006 WL 1453040, Slip No. 05-1324 (Fed. Cir. May 26, 2006) the Court of Appeals for the Federal Circuit (CAFC) agreed with the Board of Patent Appeals and Interferences (BPAI) that the poxvirus-based vaccines described in the Inglis applications were adequately described and enabled even though the specification contained no poxvirus sequences or specific examples for making a poxvirus vaccine or the phrase "incorporated by reference". Likewise, in *Capon et al. v. Eshar et al.*, Nos. 03-14480, 1481 (Fed. Cir. August 12, 2005), the CAFC reversed the BPAI and found that claims to chimeric genes composed of pieces of known genes did not need to recite the known gene sequences to satisfy the written description requirement.

As applicants have argued in the present case regarding the incorporation of "Dab1" and "Cdk5" sequences, the CAFC found that at the time of filing of the earliest Inglis application, the poxvirus genome was well known to those of ordinary skill in the art as evidenced by publication of the genome in professional journals. In view of the well known nature of the poxvirus genome, neither the BPAI or the CAFC found it necessary for the Applicant to incorporate the well known poxvirus genome into the specification by reference or otherwise. Indeed, the CAFC noted that omission of such redundant information from the specification is preferred, reiterating the familiar adage that "[a] patent need not teach, and preferably omits, what is well known in the art." citing Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534 (Fed. Cir. 1987).The terms "Dab 1" and "Cdk5" were well known in the art at the time the present application

was filed and, according to the reasoning used by the CAFC in Falkner v Inglis and Capon v Eshar, adequately describe the invention in compliance with 35 U.S.C. §112, first and second paragraphs. Therefore, Applicants respectfully submit that previous rejections made under 35 USC § 112, first and second paragraphs should not be applied to new claims 36-40.

Claims 36-38 and 40

The disclosed species are representative of the entire genus

Examiner's Arguments

In prior Office Actions, the Examiner rejected claims under 35 U.S.C. § 112, first paragraph for failure to describe a sufficient number of species to recite a genus for Cdk5 or Dab1. The Examiner asserted that the genera encompass widely variant species with respect to structure and that the three genbank nos. provided for Cdk5 and two genbank nos. provided for Dab1 were insufficient representatives of the genus. The Examiner asserted that other than the two representative species of Dab1 polypeptides, the specification failed to disclose any other additional representative species of the genus. The Examiner maintained that the disclosure of the two representative species of Dab1 polypeptides is insufficient to be representative of the attributes and features of all species encompassed by the recited genus of Dab1 polypeptides.

The Examiner maintained that the alleged novel relationship claimed by Applicants, i.e., the phosphorylation of Dab1 by Cdk5, has not been shown in all organisms that express "Cdk5" and "Dab1" polypeptides. The Examiner asserted that there is no disclosure in the specification or in the prior art of a structure-function correlation between the members of the respective genus of Cdk5 or Dab1 polypeptides such that by the mere recitation of "Cdk5" or "Dab1" one of skill can visualize the structures of all members of the respective genus.

Applicants' Arguments

Example 1 of the specification provides results obtained in the mouse model, which show Cdk5 specifically phosphorylates Dab1 at serine 491. Applicants provided evidence showing Dab1 phosphorylation on serine 491 is Cdk5 activity-dependent in a rat model as well. Applicants also provided sequence alignments for mouse, rat and

human Cdk5 and Dab1 (which were all in the public domain at the time the present application was filed) showing that both proteins are highly conserved among the three species. Applicants also showed the Dab1 sequence alignment between mouse and human is 96% identical, mouse and dog is 90% identical, mouse and bird is 89% identical, mouse and cow is 84% identical and mouse and zebrafish is 66% identical.

"Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasons substantiating the doubts so expressed." *In re Dinh-Nguten and Stenhagen*, 181 USPQ 46, 47 (Ct. Cust. & Pat. App. 1974); *see also In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Armbruster*, 185 USPQ 152, 153 (Ct. Cust. & Pat. App. 1975); *In re Bowen*, 181 USPQ 48 (Ct. Cust. & Pat. App. 1974); *In re Hawkins*, 179 USPQ 157, 162 (Ct. Cust. & Pat. App. 1973). Even at the request of Applicants throughout prosecution, the Examiner provided no scientific rational or evidentiary support for the assertion that the disclosed Cdk5/Dab1 relationship is peculiar to a single species. In the absence of such support, Applicants submit that the Examiner has failed to carry his burden for establishing prima facie nonenablement.

Even though Applicants do not provide examples showing the phosphorylation of Dab1 by Cdk5 in all organisms, Applicants have provided examples for two species of the genus and have provided support showing that Dab1 and Cdk5 are highly conserved proteins in many different species. In Falkner v. Inglis, ---F.3d---, 2006 WL 1453040, Slip No. 05-1324 (Fed. Cir. May 26, 2006) the CAFS states:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

The specification in the Inglis application focused on herpesvirus; it did not show specific examples of the claimed invention as it related to a poxvirus. However, the CAFS held that a person skilled in the art was capable of taking the claimed invention and applying it to a poxvirus. Likewise, a person of skill in the art, would have been able

to identify a Dab1 and Cdk5 protein from various species and determine if Dab1 was phosphorylated on a serine within a preferred sequence.

Having shown examples of how specific serine Dab1 phosphorylation can be used as a proxy for Cdk5 activity in mouse and rat, and showing these proteins are highly conserved in numerous species, Applicants submit that one of skill in the art would have no problem using this method to detect the activity of any Cdk5 within other species. Accordingly, Applicants respectfully submit that previous rejections made under 35 U.S.C. § 112, first paragraph for failure to describe a sufficient number of species should not be applied to new claims 36-38 and 40.

Claims 36-38 and 40

The term "preferred sequence" is definite

Examiner's Arguments

The Examiner rejected prior claims for use of the term "candidate sequence preferred by cdk5 activity" under 35 U.S.C. 112, second paragraph as being indefinite. The Examiner acknowledged the definition of the term "candidate sequence" at page 5 of the specification. However, the Examiner asserted this definition provides no indication as to the scope of those candidate sequences that are "preferred" by a "cdk5 activity" and that the term remained indefinite. The Examiner maintained that this term is indefinite in view of the indefiniteness of the term "cdk5 activity" and that the scope of candidate sequences are those that are "preferred" by cdk5 activity. It is unclear from the specification and the claims as to whether all sequences that have a serine followed by proline at the +1 position and a lysine in the +3 position are those that are "preferred" by a "Cdk5 activity" or whether only a subset of those sequences that have a serine followed by proline at the +1 position and a lysine in the +3 position are meant to be encompassed as being sequences that are "preferred" by "cdk5 activity."

Applicants' Arguments

Applicants argued and maintain that the specification specifically defines a "candidate sequence" as a sequence of amino acids which contains a serine followed by a proline in the +1 position and a lysine in the +3 position, the serine being a preferred site for Cdk5 activity (Songyanget al., Mol Cell Biol, 16:6486-6493, 1996). Songyang et al.

teach that his sequence is a distinct optimal peptide substrate for the Cdk5 kinase. Furthermore, on page 20 lines 8-18 of the specification, Applicants predicted murine Dab1 serines 491 and 515 to be Cdk5 phosphorylation sites based on sequence analysis and then conducted experiments to show their prediction was true.

Applicants have shown the terms "Cdk5" and "Dab1" were well defined and were well known by a person of skill in the art at the time of filing. Caselaw has established that what is well known in the art need not be included in a patent application as long as the applicant can show a person of skill in the art how to make and use the invention. A person of skill in the art knows the meaning of "cdk5 serine activity" and the specification clearly defines what constitutes a candidate sequence. Applicants discuss the definition of a candidate sequence and show how they determined that the serines within the two candidate sequences found in the carboxy terminal domain of Dab1 were phosphorylated by cdk5 serine activity.

Applicants respectfully submit that previous rejections made under 35 USC § 112, second paragraph should not be applied to the use of the term "candidate sequence" in new claims 36-38 and 40.

Claim 39

Examiner's Arguments

The Examiner rejected previous claims containing genbank accession numbers as being indefinite. The Examiner asserted that it is well known to one of skill in the art that sequence accession numbers are updated by modifying the sequence of a particular accession number. The Examiner stated that there is no way to know with certainty that the sequence of genbank accession numbers will not change. Genbank accession numbers are not static, but can change by revision. The Examiner provided an example of the revision history for Accession Number X761041 (a protein unrelated to this application).

Applicants' Arguments

The U.S. Patent Office has previously accepted the use of genbank accession numbers in claims to refer to biological sequence information known and available in the prior art. For example, U.S. Patent No. 6,770,742, issued August 3, 2004 claims a fibroblast growth factor receptor-4 by reference to a genbank accession number. The

FGFR-4 sequence is not listed in the sequence listing, thus there is no SEQ ID qualifier for the FGFR-4 receptor. Furthermore, the revision history for this genbank accession number shows that it was revised no less than 7 times. Additional granted patents in which the patentee was allowed to refer to nucleotide or amino acid sequences according to genbank numbers in the claims include, but are not necessarily limited to, U.S. Patent Nos. 6,949,342; 6,943,006; 6,890,572 and 6,667,065.

Since there appears to be no per se rule against the use of genbank accession numbers in claims, Applicants ask that the Examiner reconsider and allow the use in this instance where the sequence itself does not go to the heart of the invention, but is simply useful information for understanding the invention.

In a copy of the revision history for Accession Number X761041 provided by the Examiner in the Office Action dated 8/2/05, each date the accession number was revised is clearly shown. Furthermore, a link is provided so that one can review the contents of the accession number for each date prior to a revision. Since a person of skill in the art knows the filing date of the present application, that person can easily access the sequence in genbank that was known at that time. Therefore, the use of genbank accession numbers in the claims is clear and definite. Furthermore, any changes that might be made to this sequence would not be expected to change the characteristics of the Cdk5 or Dab1 proteins which are important in the context of the claimed invention.

Applicants respectfully submit that previous rejections made under 35 USC § 112, second paragraph, based on the assertion that the use of genbank numbers renders the claims indefinite, should not be applied to new claim 39.

Claim 40

Examiner's Arguments

In an attempt to address the Examiner's rejection of previous claims stating that a genus requires a precise definition, such as structure, formula or chemical name of the claimed subject matter to sufficiently distinguish it from other materials, Applicants amended the claims to require that the Dab1 protein include SEQ ID NO:3. Support for SEQ ID NO:3 can be found on page 3, lines 25 – 29 and page 15, lines 16-17.

The Examiner rejected the claims that incorporated SEQ ID NO:3 as a structural limitation for Dab1 proteins under 35 U.S.C. 112, first paragraph for inserting new matter. The Examiner asserted that while the disclosure provides support for the peptide of SEQ ID NO:3, it fails to support the recited genus of Dab1 polypeptides comprising SEQ ID NO:3. The Examiner maintained that while all members of the genus of Dab1 polypeptides comprise the structural feature of the 14 amino acid peptide of SEQ ID NO:3, this structural feature does not constitute a "substantial portion" of the genus of recited Dab1 polypeptides. Thus, the Examiner maintained the specification failed to adequately describe the claimed invention.

Applicants' Arguments

SEQ ID NO:3 comprises 14 amino acids found in the c-terminal portion of the Dab1 protein in several different species including mice, rats, humans, birds, dogs and cows. Proteins other than Dab1, even closely related proteins such as Dab2, do not share this sequence. SEQ ID NO:3 is provided as a common structural reference for the genus of Dab1 proteins to supplement the distinguishing features of Dab1 noted in the specification. A peptide having the sequence of SEQ ID NO:3, as shown in the specification, was used as an antigen to generate an antibody that binds to Dab1. The use of this peptide as an antigen reveals to one of skill in the art that this is a sequence that is characteristic of Dab 1 and useful for distinguishing Dab1 from other proteins. Therefore, inclusion of SEQ ID NO:3 in the claims as a feature of Dab 1 is fully supported by the specification and is not new matter.

Applicants respectfully submit that the previous rejection made under 35 U.S.C. § 112, first paragraph, for inserting new matter, should not be applied to new claim 40.

Specification/Informalities and 35 U.S.C § 112, First Paragraph Rejection

The Examiner objected to the amendment filed 4/25/2005 under 35 U.S.C. 132(a) for introducing new matter into the disclosure. The Examiner asserts that according to MPEP § 608.01(p) incorporation by reference of material in a non-patent document "must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) Clearly identify the referenced patent, application, or publication."

See 37 § 1.57(b). Furthermore the Examiner states that MPEP § 608.01(p) further states, "[i]f a reference to a document does not clearly indicate an intended incorporation by reference, examination will proceed as if no incorporation by reference statement has been made and the Office will not expend resources trying to determine if an incorporation by reference was intended."

The Examiner rejected Claims 1, 4-8, 10-11, 13-15, 32 and 35 as failing to comply with the written description requirement. The Examiner asserts that the claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Prior to making the present objection and rejection, the Examiner previously determined that SEQ ID NOs:4 and 5 were intended to be incorporated by reference based on the inclusion of the appropriate genback numbers. The Examiner withdrew an objection in the 8/22/05 Office Action, stating that the disclosed GenBank Accession Number in the specification is considered to be an inherent "incorporation by reference", and proceeded to examine the claims based on the inclusion of SEQ ID NO:4 (mouse Dab1). On page 9 of the Office Action dated 2/21/06, the Examiner allowed a claim that incorporated SEQ ID NO:4 and indicated that 2 other claims, one that incorporated SEQ ID NO:4 and another that incorporated SEQ ID NO:5, would be allowed if written in independent form. However, in the Office Action dated 5/1/06, the Examiner reconsidered this determination and is now rejecting the claims citing 37 C.F.R.§1.57 and MPEP § 608.01(p). The Examiner asserts the originally filed disclosure does not provide support for SEQ ID NO:4 and SEQ ID NO:5 which are included in Claims 1, 32 and 35 based on the fact that the root words "incorporate" and "reference" do not appear in the specification. According to the Examiner, even though the genbank accession numbers are included in the definition of Dab1, this is insufficient support for incorporating the sequences associated with these accession numbers (i.e. SEQ ID Nos. 4 and 5) because the specification does not specifically state the accession numbers are to be incorporated by reference.

Applicants respectfully disagree with the preceding objection and rejection of the Claims. The regulation cited to support this rejection, 37 C.F.R.§1.57, was added on Sept.

21, 2004 and became effective Oct. 21, 2004, well after the February 19, 2002 filing date of the present application. Furthermore, MPEP § 608.01(p) was not amended until Oct. 21, 2004 to include the language stated in the above objection by the Examiner. A patent application should not be faulted for failing to adhere to rules established well after its filing date.

However, even if Applicants are held to this standard, 37 C.F.R. § 1.57 (g)(1) does allow correction to comply with paragraph (b)(1) of this section if the application as filed clearly conveys an intent to incorporate the material by reference. 37 C.F.R. § 1.57 (g)(2) states that [a] correction to comply with paragraph (b)(2) of this section is permitted for material that was sufficiently described to uniquely identify the document.

On page 4, lines 24-25 of the specification, Applicants specifically define Dab1 proteins as including proteins cloned from genbank accession numbers 3288851 and 1771281. As Applicants argued earlier in its response dated 6/16/05 to the Examiner's assertion made in the Advisory Action mailed 5/18/05, including these genbank numbers as part of the definition of Dab1 reflects Applicants' intent for these publications to be incorporated by reference. Applicants also indicated during prosecution that the sequences incorporated into the specification were the sequences found in the genbank accession numbers at the time of filing of the application. Thus, Applicants have fulfilled the requirements of 37 § 1.57 (g)(1) and (g)(2).

In light of the arguments presented above, Applications have overcome the objection and rejection. Reconsideration and withdrawal of such are respectfully requested.

Conclusion

It is believed that the objection and rejection of Claims 1, 4-8, 10-11, 13-15, 32 and 35 have been overcome. Given the arguments stated above for new claims 36-40, Applicants have addressed the Examiner's rejections of claims previously found in the application that were similar to the new claims and request allowance of the new claims.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow

consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 501968.

Respectfully submitted,

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